FUNCTIONAL MICROSTIMULATION OF THE LUMBOSACRAL SPINAL CORD

Contract NIH-NINDS-No1-NS-2-2342

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ABSTRACT

The main aim of this contract is to test the idea that intraspinal microstimulation (ISMS) can be used selectively to excite neurons that activate the bladder detrusor muscle while simultaneously stimulating interneurons which inhibit motoneurons of the external urethral sphincter (EUS). If this reciprocal action works well enough to produce bladder voiding after spinal-cord-injury (SCI), it could form the basis of a neuroprosthesis that would restore bladder control without the need for transection of sensory nerve roots of the spinal cord (dorsal rhizotomies).

In this third quarter of operation the following was achieved:

1) Stability of a long-term ISMS electrode implant was demonstrated. In a cat chronically implanted with ISMS electrodes on 2 October 2002, bladder contractions and voiding were elicited by ISMS in the awake animal with parameters that have remained fairly stable for over 3 months.

2) Chronic implants of ISMS microwire arrays were performed in two cats.

3) A new, more compact headpiece assembly was designed and tested in these two new implants. The headpiece was convenient to implant and assuming there is no structural or electrical failure in it in subsequent weeks and months, it will be suitable for sealing and subcutaneous stowage.

4) The end of the bladder catheter was modified slightly from the previous designs. This greatly facilitated the implantation procedure. The length of the intravesicular portion of the catheter appears to be crucial for reliable long-term performance.

5) In the chronic implants to date the following effects of ISMS have been noted:

- Increases in bladder pressure of up to 50 mm Hg can be elicited reproducibly by ISMS in the awake animal.
- Voiding with very small residual volumes has been achieved over the last two months in the first cat to be implanted. There was evidence for both direct and triggered voiding responses, depending on stimulus levels.
- Stimulus rates of up to 100/s may be preferable in ISMS to the lower rates (e.g. 25/s) normally used in sacral root stimulators.

PROGRESS IN THIS QUARTER

METHODS

Anesthesia and Monitoring of Vital Signs

Three male adult cats were used in the experiments, one of which was chronically implanted with an ISMS array and bladder catheter in the previous reporting quarter (Mick 01Oct02). All three implant surgeries were performed in a fully-equipped operating room with sterile equipment and procedures. The cats were anesthetized with 2-3% isoflurane in carbogen: (95% O_2, 5% CO_2), 1.5 L/min. Anesthesia was maintained through a pediatric endotracheal tube. An intravenous catheter was inserted in the cephalic vein and a saline drip was delivered throughout the procedure. The cats' body temperature was maintained using heating pads and lamps. ISMS microwires were implanted in the sacral spinal cord, a catheter was implanted into the bladder, and in two cats, in-dwelling wires were implanted into the urethra for the purposes of measuring EMG or to allow intra-urethral stimulation.

Implantation of Urinary Tract Monitoring Devices

The silastic bladder catheter described in the last report and shown again in Fig. 1A has remained functional for 4 months. It shows no obvious increase in resistance to flow during bladder emptying or filling and the pressure recordings obtained during ISMS have remained stable. However the cat implanted with this catheter (Mick 01Oct02) has continued from the outset to have a low tolerance to bladder filling and urinates frequently (threshold for eliciting voluntary voiding 8-11 ml). We have suspected that the portion of the catheter extending into the bladder and/or the retaining cone inside the bladder may cause irritation to the internal bladder wall. Therefore in the last two implants we omitted the cone and shortened the intravesicular portion of the catheter.

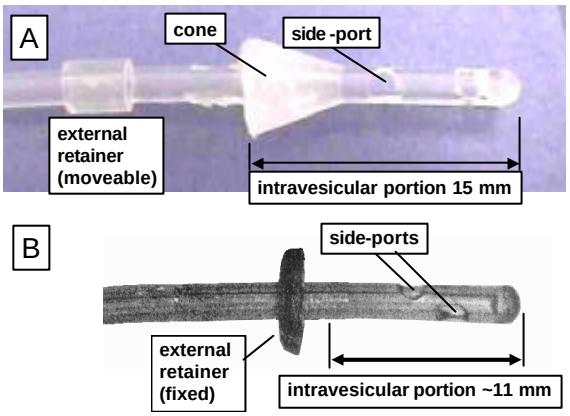

Figure 1. A) Tip of bladder catheter implanted in cat Mick 01Oct02, showing intravesicular retaining cone and external retaining sleeve. B) Tip of bladder catheter implanted in cat Pascal 27jan03 with shorter intravesicular portion and external retaining disk only.

Implantation of the catheters in the two new cats (Perry 15Jan03, Pascal 27Jan03) was performed in a similar way to that described in the previous report, except that the introducing stylette was threaded inside the catheter from its far end rather than being introduced into the side-port close to the tip. This avoided the stylette and cone portion of the catheter being side-by-side during insertion into the bladder, which had created difficulties, especially when the stylette was withdrawn.

For implantation, the bladder was exposed through a midline abdominal incision. The end of the catheter was inserted into the bladder through a puncture hole created with a 16G hypodermic needle. The stylette was withdrawn, leaving the end of the catheter in the bladder. A purse-string suture (4/0 prolene monofilament) previously placed around the entry point was tightened and knotted around the catheter (two purse-string sutures were placed in cat Pascal 27Jan03). The external retaining disk of the catheter was sewn to the bladder wall with four separate sutures to ensure that the catheter stayed in place. The bladder was filled with 60ml saline and squeezed, to check for leaks around the catheter. The abdominal musculature was sutured closed with 3/0 catgut, the catheter emerging at the rostral end. A trochar was used to draw the catheter subcutaneously to the cat's head. The abdominal skin was sutured closed with 4/0 prolene.

Intraurethral EMG electrodes and pressure measurements

The Luer port at the headpiece end of the bladder catheter was connected to a Neurolog NL108D4/10 dome and NL108T4 isolated pressure transducer. The pressure signal was low-pass filtered at 30 Hz and sampled at 400 samples/s using a CED Power 1401 (Cambridge, UK) laboratory interface linked to a personal computer running CED Signal 2.1 software. The data were stored on the computer's hard drive for later analysis.

ISMS: Locating targets in the Sacral Spinal Cord

The bladder was first emptied, then refilled with 30 ml saline via the indwelling catheter. The optimal location for the ISMS electrode array was established as described in previous reports: a series of penetrations through the dura was performed with a search electrode (30 µm stainless steel microwire, 3.5 mm depth). Short (~0.5s) pulse trains of up to 250µA at 25/s or 50/s were applied. Bladder pressure was monitored with the Neurolog system as described above. The aim was to establish the point in the spinal cord from which the largest increase in bladder pressure could be elicited. This was assumed to be close to the centre of the bladder preganglionic nucleus. Additional useful indicators of location with respect to relevant motoneuron pools included contractions of perineal muscles, tail muscles, intrinsic toe muscles and hamstrings muscles. When the location eliciting the greatest increase in bladder pressure (e.g. 40 mm Hg) was determined, an

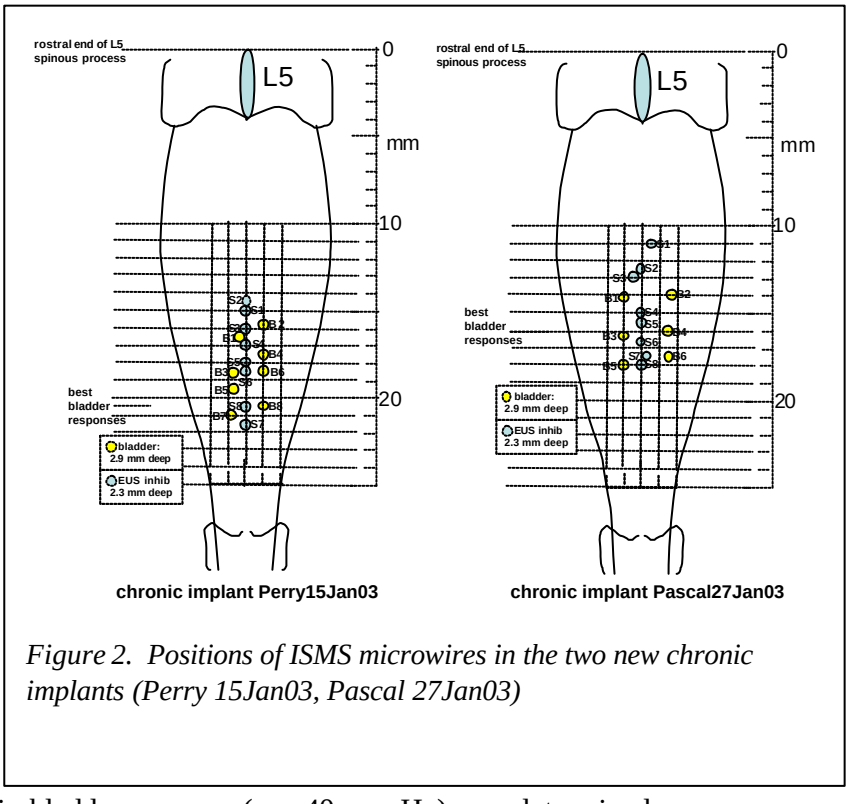

Figure 2. Positions of ISMS microwires in the two new chronic implants (Perry 15Jan03, Pascal 27Jan03)

8/0 ophthalmic suture was sewn into the dura mater to act as a marker for the placement of the microwire array (arrows in Fig. 2).

The prefabricated ISMS array (30 µm dia. Platinum-iridium microwires) was then fixed in place by tacking it to the L4 or L5 spinous process, embedding this portion in dental acrylic, and then inserting each microwire into the spinal cord manually. If a microwire was not sharp enough to penetrate the dura easily, the surface of the dura was scratched or a small hole was made in it with a 30G dental needle. For each microwire targeting the bladder preganglionic nucleus (Fig. 2, locations b1-b6) the lateral distance from the midline and the depth of insertion were adjusted so that test stimulus trains evoked the maximal increase in bladder pressure. A custom-made multi-channel microstimulator was used to deliver ISMS through each electrode in turn (Prochazka et al., 2002). Typically microwires targeting the bladder preganglionic neurons evoked maximal bladder contractions at depths of 2.8 to 3.2 mm relative to the dural surface and 1 to 1.5 mm lateral to the midline. Microwires targeting the EUS inhibitory region were inserted 2.0-2.5 mm deep to the dural surface in or close to the midline. The precise coordinates of each electrode as judged at surgery is detailed in table 1. Confirmation of these coordinates will be done at autopsy.

When all the microwires were inserted, small droplets of cyanoacrylate glue (Loctite 414 Superbonder) were released onto their entry points from a 1 ml syringe with a 25G needle whose tip had been broken off. Two layers of plastic thin-film were placed over the entire array and tacked to the dura around the edges. The back wound was then sutured closed in layers with the use of 3/0 catgut for the paravertebral muscles and lumbodorsal fascia, and 4/0 prolene for the skin. The microwire connector was pulled subcutaneously to the headpiece with a custom-made trochar.

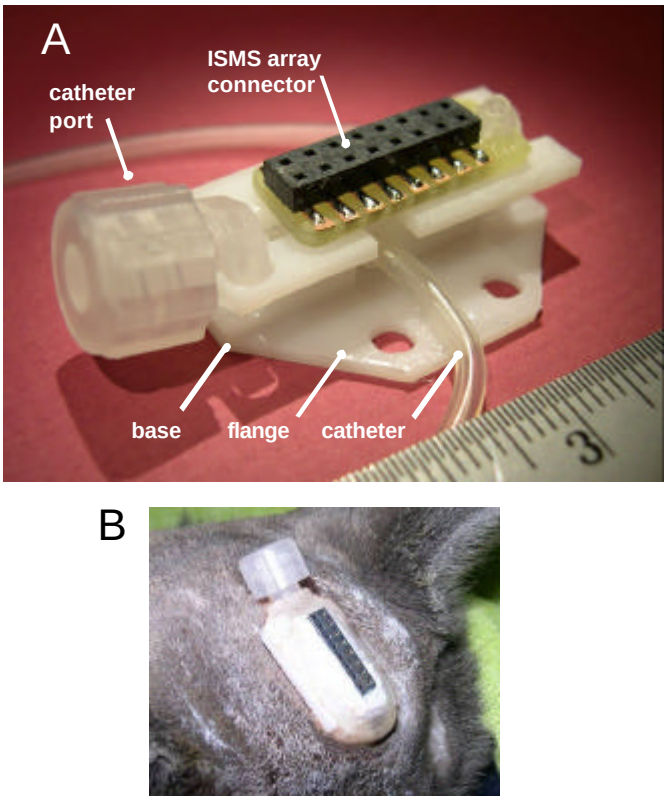

Figure 3 Headpiece (Perry 15Jan03, Pascal 27Jan03) A) Plastic base B) Headpiece assembly with catheter and ISMS connector in place and sealed with acrylic.

Head-piece

The headpiece in the two latest implants was a new design (see Fig. 3). The main new feature of the headpiece was the use of a small, milled plastic base, which was first attached to the skull with four screws. The Luer port of the bladder catheter was placed into a form-fitting recess and bonded in place with dental acrylic. The connector from the

ISMS array was then glued to the top surface of the plastic base with the use of Loctite 7113 activator and 620 superbonder. Finally, the skin was pulled up onto the bottom flange to form a tight seal around the assembly (Fig. 3B).

RESULTS

ISMS in the awake cat

1. Stability

Fig. 4 shows two trials in cat Mick 01Oct02 in which ISMS through a single microwire (B1: location shown in lower part of the figure) evoked increases in bladder pressure of about 15 mm Hg. These trials were obtained on day 3 after the implant, and day 115 respectively. The stimulus parameters were similar, and similar pressure increments were evoked. There were no orienting or aversive responses to stimulation on either occasion.

The results obtained so far across all electrodes in this cat indicate that the responses evoked by about half of the electrodes remained very stable over time as illustrated in Fig. 4. The other half

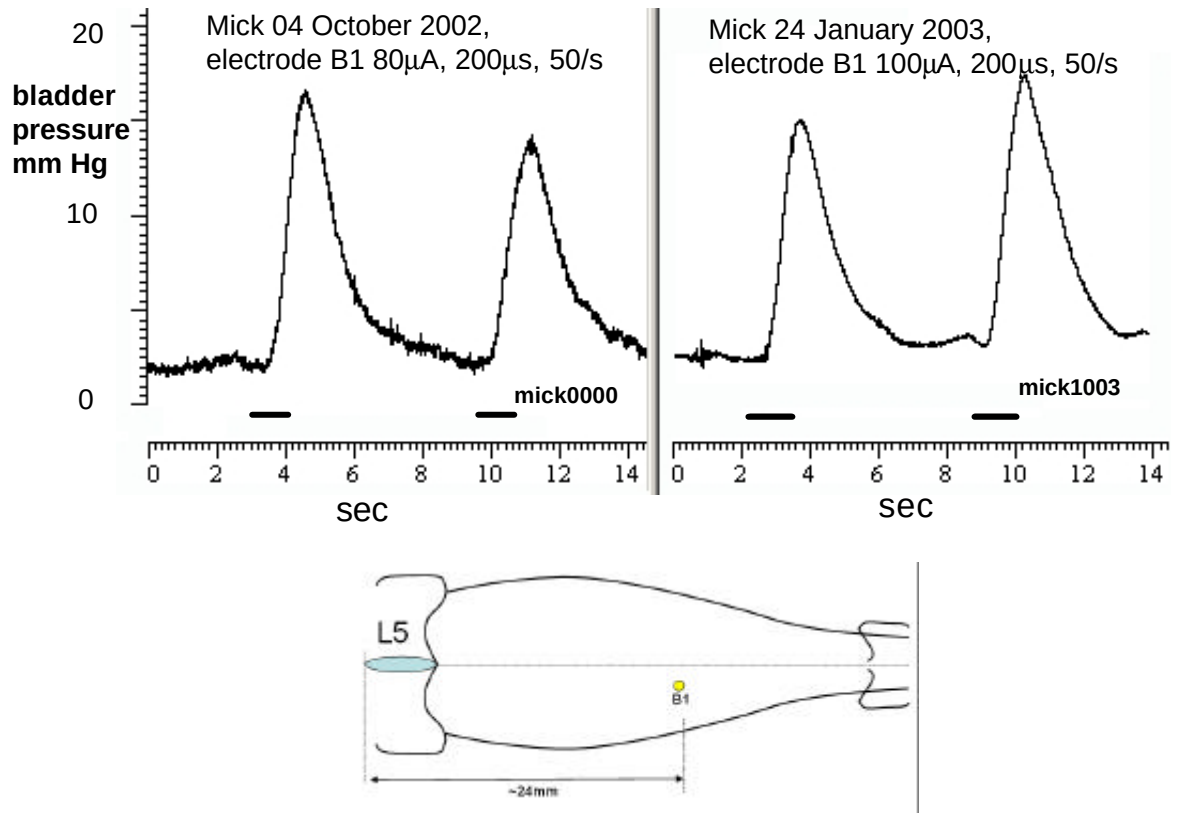

Figure 4 Stability of ISMS microwires. Bladder contractions evoked in cat Mick 01Oct02 from the most rostral microwire targeting the bladder preganglionic nucleus (location of electrode shown in lower panel). Two trials separated by 112 days with similar stimulation parameters. .

showed changes in the responses they evoked over the first 4-6 weeks after implantation, but responses remained stable after this settling-in period.

2. Direct and triggered voiding.

Fig. 5 shows a trial in which ISMS evoked almost complete voiding. ISMS was delivered through microwires implanted in the region of the bladder preganglionic nucleus. Three short bursts of ISMS (stimulus parameters shown in the Figure) were followed by sustained stimulation for about 15 sec. The sustained stimulation evoked a large increase in bladder pressure. The volume trace was obtained using the weigh-pan system described in Quarterly Report #2. The cat's hind-quarters were held over a funnel which collected the urine and

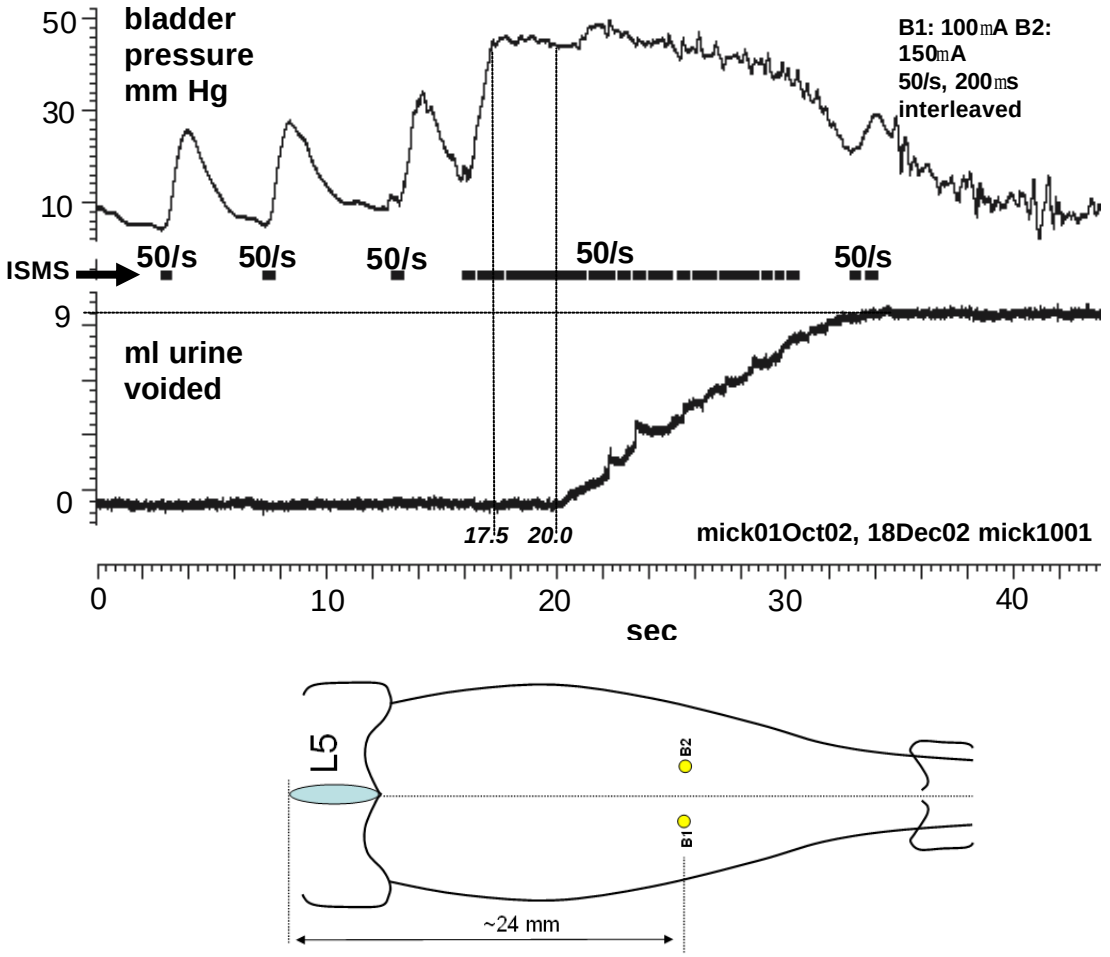

Figure 5 Voiding elicited by ISMS in awake cat. Trains of ISMS pulses delivered via bladder preganglionic nucleus electrodes B1 and B2: bottom panel shows locations. Residual volume after voiding was confirmed as 1.5 ml. First vertical dotted line at17.5s indicates when bladder pressure reached maximum. Second vertical line at 20s shows onset of voiding. The2.5s delay corresponds to the time taken for urine to flow into the collecting pan.

delivered it to the weigh-pan. The 2.5s delay between peak pressure being reached and the onset of the increase in the volume signal is attributable to the time taken for urine to flow through the funnel into the weighing pan. The bladder pressure profile reached a maximum 1.3s after the onset of the sustained stimulus train and remained fairly constant for the next 10 seconds. This suggests that the ISMS train was directly causing the voiding episode, rather than triggering a reflexive or voluntary micturition response. In the latter case, we would have expected to see an additional surge of pressure, an example of which is shown in Fig. 6.

In this trial, a lower stimulus rate (25/s) was used than in the trial of Fig. 5 (50/s). The ISMS evoked an initial rise in bladder pressure of about 20 mm Hg. This did not produce voiding. However at the 6s mark, a secondary rise in bladder pressure occurred and a complete voiding of the bladder ensued. Evidently stimulation at 25/s was insufficient to evoke the voiding response alone. The secondary surge was accompanied by a postural shift in the animal, suggesting that it was a triggered voluntary or reflexive voiding response. Note that the bladder pressure remained high after stimulation ceased, again indicating that voiding was a triggered reaction rather than a direct result of the stimulation.

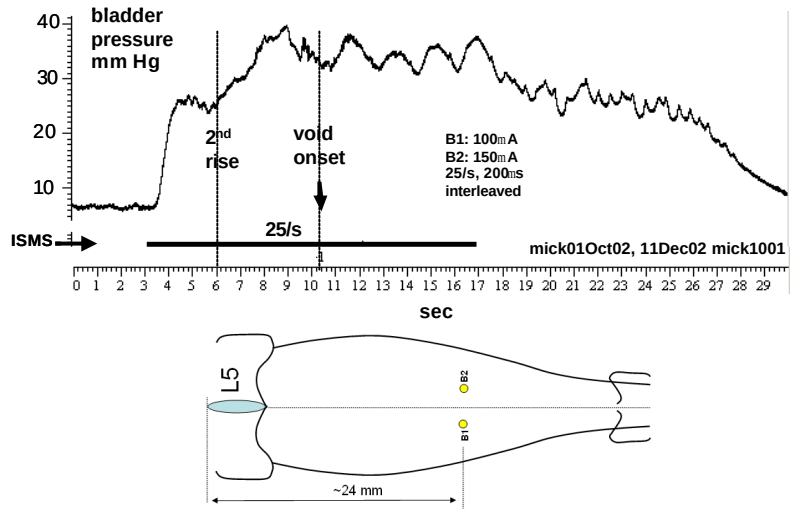

Figure 6. Voiding elicited by ISMS in awake cat. In this case the stimulus rate was 25/s per channel. The stimulus train elicited an initial rise in bladder pressure of about 20 mm Hg at the 4s mark, followed by a secondary rise at 6s with ensuing void commencing at 10.5s (visual observation entered on keyboard: see "1" marker on trace just above time axis).

3. Stimulation frequency and pattern.

Fig. 7 shows a trial in which the bladder pressures evoked by stimulus rates of 25/s and 50/s were compared (interleaved stimulation, electrodes B1 and B2). 50/s stimulation elicited larger increases 25/s. Sustained stimulation over several seconds evoked larger peak pressures than 0.5s bursts of stimulation and in this trial complete voiding occurred. We also found that stimulation at 100/s evoked even larger increases in bladder pressure than stimulation at 50/s. In the Brindley Finetech sacral root stimulator, 25/s is the stimulus rate commonly used. Higher rates, and sustained periods of stimulation may be more effective in intraspinal microstimulation.

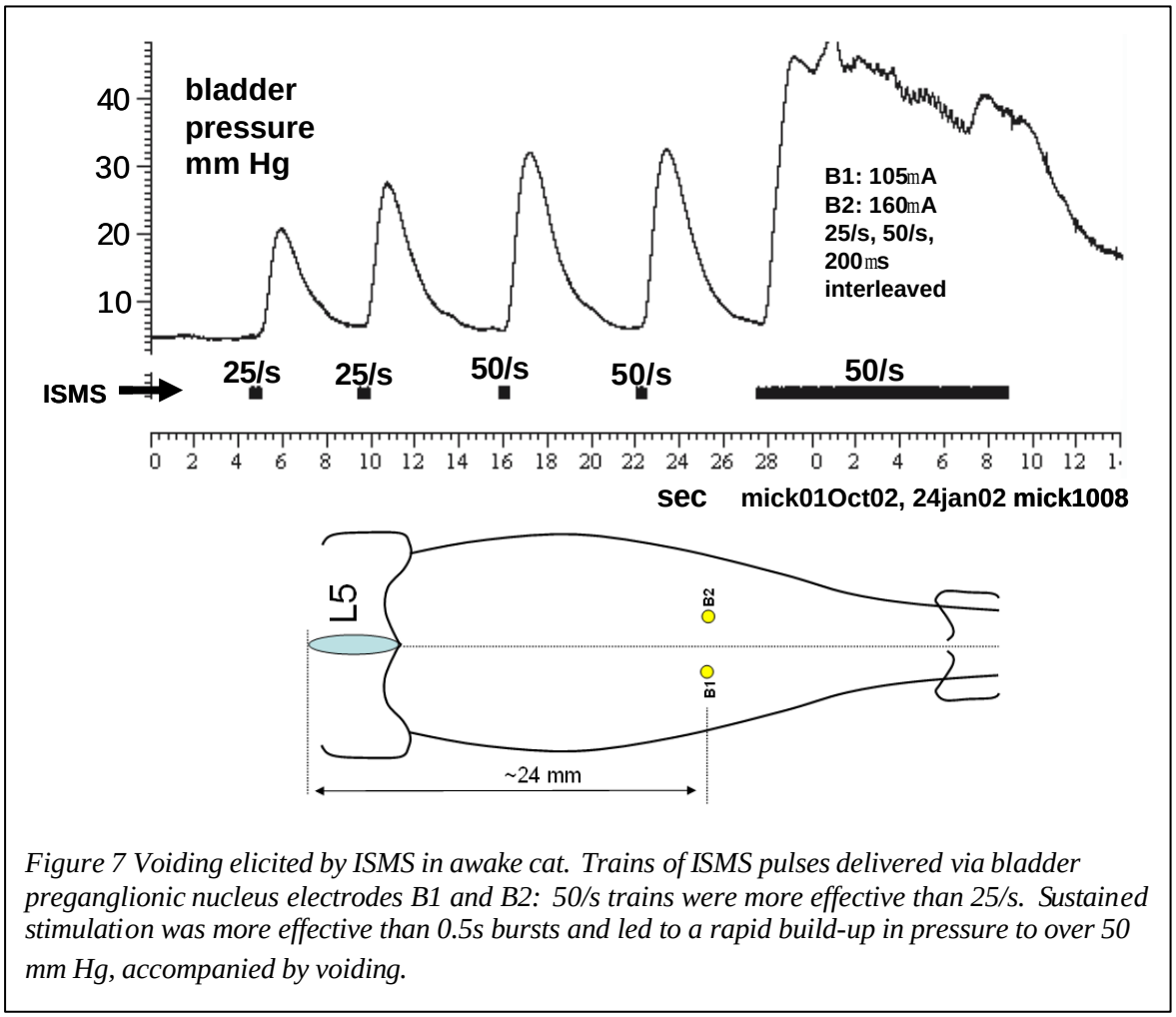

Figure 7 Voiding elicited by ISMS in awake cat. Trains of ISMS pulses delivered via bladder preganglionic nucleus electrodes B1 and B2: 50/s trains were more effective than 25/s. Sustained stimulation was more effective than 0.5s bursts and led to a rapid build-up in pressure to over 50 mm Hg, accompanied by voiding.

DISCUSSION

The main technical developments this quarter were the improved bladder catheter and a modular head-piece. The main scientific findings were 1) that responses evoked by chronically implanted ISMS microwires can remain stable for several months. 2) Voiding can be elicited by ISMS in bladder preganglionic regions alone. Strong stimulation appeared to evoke voiding directly. Weaker stimulation appeared to trigger voluntary or reflexive voiding responses. 3) Stimulation at rates up to 100/s may be desirable in ISMS.

Regarding the observations of voiding responses to ISMS in the normal awake cat, it will be interesting to see whether similar responses will be elicited from the same electrodes after chronic spinalization.

PLANS FOR THE NEXT QUARTER

1) S trials in the most recently implanted cats (Perry and Pascal).

2) Three further chronic ISMS implants in Edmonton
- Characterize the types of bladder and sphincter responses elicited by multichannel ISMS in the sacral region in the awake animal, particularly in relation to bladder volume.
- Concentrate on eliciting urethral inhibition, either with ISMS or intra-urethral stimulation in combination with bladder contraction to elicit voiding.

3) Spinalization of a chronically implanted cat (Mick01Oct02), with ISMS trials post-spinalization. Comparisons will be made between responses evoked before and after spinalization.

ACKNOWLEDGEMENTS

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REFERENCES

Prochazka A, Mushahwar VK, Downie JW, Shefchyk SJ (2002) Functional microstimulation of the lumbosacral spinal cord. In:, pp 1-19: NIH-NINDS contract # 1-NS-2-2342.